

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of inhibiting restenosis and selectively inhibiting pain/inflammation and/or spasm in a vascular procedure, comprising delivery during the vascular procedure of a solution of a plurality of agents selected from the group consisting of pain/inflammation inhibitory agents, spasm inhibitory agents and restenosis inhibitory agents in a liquid carrier, the agents being selected to act on a plurality of differing molecular targets, the agents including at least one restenosis inhibitory agent, wherein the solution is applied locally and perioperatively to an operative vascular site.
2. The method of Claim 1, wherein the perioperative application of the solution comprises intraprocedural application together with preprocedural and/or postprocedural application of the solution.
3. The method of Claim 1, wherein the solution is adapted to be locally applied to the operative vascular site in the absence of metabolic transformation.
4. The method of Claim 1, wherein the solution is adapted to be continuously applied to the operative vascular site.
5. The method of Claim 1, wherein the solution is adapted to be applied by irrigation of the operative vascular site.
6. The method of Claim 1, wherein the restenosis inhibitory agent is selected from the group consisting of: antiplatelet agents including thrombin inhibitors and receptor antagonists, purinoceptor antagonists, thromboxane inhibitors and receptor antagonists and platelet membrane glycoprotein receptor antagonists; inhibitors of cell adhesion molecules, including selectin inhibitors and integrin inhibitors; anti-chemotactic agents; interleukin receptor antagonists; and intracellular signaling inhibitors including protein kinase C inhibitors and protein tyrosine kinase inhibitors, modulators of intracellular protein tyrosine phosphatases, inhibitors of src homology₂ domains, and calcium channel antagonists.
7. The method of Claim 1, wherein the restenosis inhibitory agent is selected from the group consisting of: (a) antiplatelet agents selected from the group consisting of (i) direct thrombin inhibitors and receptor antagonists, (ii) purinoceptor receptor antagonists, (iii) thromboxane inhibitors and receptor antagonists and (iv) platelet membrane glycoprotein receptor antagonists; (b) inhibitors of cell adhesion

molecules, including (i) selectin inhibitors and (ii) integrin inhibitors; (c) anti-chemotactic agents; (d) interleukin receptor antagonists; and (e) intracellular signaling inhibitors selected from the group consisting of (i) protein kinase C inhibitors and protein tyrosine kinase inhibitors, (ii) modulators of intracellular protein tyrosine phosphatases, and (iii) inhibitors of src homology₂ domains.

8. The method of Claim 1, wherein each of the plurality of agents in the solution applied is included at a concentration that is sufficient to provide a level of inhibitory effect at the operative vascular site when locally applied, and that is less than a concentration that would be required to provide the same level of inhibitory effect at the operative vascular site if applied systemically.

9. The method of Claim 1, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 100,000 nanomolar.

10. The method of Claim 1, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 10,000 nanomolar.

11. The method of Claim 1, wherein each of the plurality of agents in the solution is included at a concentration of from 0.1 to 10,000 times the dissociation constant of the agent.

12. The method of Claim 1, wherein each of the plurality of agents in the solution is included at a concentration of from 1.0 to 1,000 times the dissociation constant of the agent.

13. The method of Claim 1, wherein the liquid carrier comprises an irrigation fluid.

14. The method of Claim 1, wherein the liquid carrier is selected from the group consisting of a biocompatible solvent, a suspension, a polymerizable or non-polymerizable gel, a paste and a salve.

15. The method of Claim 1, wherein the solution includes at least one spasm inhibitory agent.

16. The method of Claim 15, wherein the at least one spasm inhibitory agent is selected from the group consisting of: serotonin₂ receptor subtype antagonists; tachykinin receptor antagonists; nitric oxide donors; ATP-sensitive potassium channel openers; calcium channel antagonists; and endothelin receptor antagonists.

17. The method of Claim 16, wherein the at least one spasm inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin₂ receptor antagonists; 0.1 to 10,000 nanomolar for tachykinin receptor antagonists; 1.0 to 10,000 nanomolar for nitric oxide donors; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; 1.0 to 10,000 nanomolar for calcium channel antagonists; and 0.01 to 100,000 nanomolar for endothelin receptor antagonists.

18. The method of Claim 1, wherein the solution includes at least one pain/inflammation inhibitory agent.

19. The method of Claim 18, wherein the at least one pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin₁ receptor subtype antagonists and neurokinin₂ receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA₂ isoform inhibitors and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 receptor subtype antagonists and eicosanoid EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B₄ receptor subtype antagonists and leukotriene D₄ receptor subtype antagonists; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinceptor agonists and antagonists including P_{2Y} receptor agonists and P_{2X} receptor antagonists; and ATP-sensitive potassium channel openers.

20. The method of Claim 19, wherein the at least one pain/inflammation inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.01 to 1,000 nanomolar for histamine receptor antagonists; 0.1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin₁ receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin₂ receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for PLA₂ isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B₄ receptor subtype antagonists; 0.1 to 500

nanomolar for μ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for δ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for κ -opioid receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; and 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers.

21. The method of Claim 1, wherein the solution comprises at least one additional restenosis inhibitory agent.

22. The method of Claim 1, wherein the restenosis inhibitory agent is included at a concentration of: 0.00003 to 20,000 nanomolar for antiplatelet agents; 0.1 to 10,000 $\times K_d$ for inhibitors of cell adhesion molecules; 0.1 to 100,000 nanomolar for protein kinase C inhibitors; and 0.1 to 100,000 nanomolar for protein tyrosine kinase inhibitors.

23. The method of Claim 1, wherein the restenosis inhibitory agent is included at a concentration of: 2.0 to 2,000 nanomolar for thrombin inhibitors or receptor antagonists; 1.0 to 1,000 $\times K_d$ for platelet membrane glycoprotein receptor antagonists; 1 to 1,000 nanomolar for protein kinase C inhibitors; and 100 to 20,000 nanomolar for protein tyrosine kinase inhibitors.

24. A method of inhibiting restenosis in a vascular procedure, comprising delivery during the vascular procedure of a solution of a plurality of restenosis inhibitory agents in a liquid carrier, the agents being selected to act on a plurality of differing molecular targets, wherein the solution is applied locally and perioperatively to an operative vascular site.

25. The method of Claim 24, wherein the perioperative application of the solution comprises intraprocedural application together with preprocedural and/or postprocedural application of the solution.

26. The method of Claim 24, wherein the solution is adapted to be locally applied to the operative vascular site in the absence of metabolic transformation.

27. The method of Claim 24, wherein the solution is adapted to be continuously applied to the operative vascular site.

28. The method of Claim 24, wherein the solution is adapted to be applied by irrigation of the operative vascular site.

29. The method of Claim 24, wherein the restenosis inhibitory agents are selected from the group consisting of: antiplatelet agents including thrombin inhibitors and receptor antagonists, purinoceptor antagonists, thromboxane inhibitors and receptor

antagonists and platelet membrane glycoprotein receptor antagonists; inhibitors of cell adhesion molecules, including selectin inhibitors and integrin inhibitors; anti-chemotactic agents; interleukin receptor antagonists; and intracellular signaling inhibitors including protein kinase C inhibitors and protein tyrosine kinase inhibitors, modulators of intracellular protein tyrosine phosphatases, inhibitors of src homology₂ domains, and calcium channel antagonists.

30. The method of Claim 24, wherein the restenosis inhibitory agents are selected from the group consisting of: (a) antiplatelet agents selected from the group consisting of (i) direct thrombin inhibitors and receptor antagonists, (ii) purinoceptor receptor antagonists, (iii) thromboxane inhibitors and receptor antagonists and (iv) platelet membrane glycoprotein receptor antagonists; (b) inhibitors of cell adhesion molecules, including (i) selectin inhibitors and (ii) integrin inhibitors; (c) anti-chemotactic agents; (d) interleukin receptor antagonists; and (e) intracellular signaling inhibitors selected from the group consisting of (i) protein kinase C inhibitors and protein tyrosine kinase inhibitors, (ii) modulators of intracellular protein tyrosine phosphatases, and (iii) inhibitors of src homology₂ domains.

31. The method of Claim 24, wherein each of the plurality of agents in the solution applied is included at a concentration that is sufficient to provide a level of inhibitory effect at the operative vascular site when locally applied, and that is less than a concentration which would be required to provide the same level of inhibitory effect at the operative vascular site if applied systemically.

32. The method of Claim 24, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 100,000 nanomolar.

33. The method of Claim 24, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 10,000 nanomolar.

34. The method of Claim 24, wherein each of the plurality of agents in the solution is included at a concentration of from 0.1 to 10,000 times the dissociation constant of the agent.

35. The method of Claim 24, wherein each of the plurality of agents in the solution is included at a concentration of from 1.0 to 1,000 times the dissociation constant of the agent.

36. The method of Claim 24, wherein the liquid carrier comprises an irrigation fluid.

37. The method of Claim 24, wherein the liquid carrier is selected from the group consisting of a biocompatible solvent, a suspension, a polymerizable or non-polymerizable gel, a paste and a salve.

38. The method of Claim 24, wherein the restenosis inhibitory agents are included at a concentration of: 0.00003 to 20,000 nanomolar for antiplatelet agents; 0.1 to 10,000 $\times K_d$ for inhibitors of cell adhesion molecules; 0.1 to 100,000 nanomolar for protein kinase C inhibitors; and 0.1 to 100,000 nanomolar for protein tyrosine kinase inhibitors.

39. The method of Claim 24, wherein the restenosis inhibitory agents are included at a concentration of: 2.0 to 2,000 nanomolar for thrombin inhibitors or receptor antagonists; 1.0 to 1,000 $\times K_d$ for platelet membrane glycoprotein receptor antagonists; 1 to 1,000 nanomolar for protein kinase C inhibitors; and 100 to 20,000 nanomolar for protein tyrosine kinase inhibitors.

40. A solution for use in the preemptive inhibition of restenosis, and selectively for preemptively inhibiting pain/inflammation and/or spasm, during a vascular procedure, comprising a plurality of agents selected from the group consisting of pain/inflammation inhibitory agents, spasm inhibitory agents and restenosis inhibitory agents in a liquid carrier, the agents being selected to act on a plurality of differing molecular targets, the solution including at least one restenosis inhibitory agent selected from the group consisting of: (a) antiplatelet agents selected from the group consisting of (i) direct thrombin inhibitors and receptor antagonists, (ii) purinoceptor receptor antagonists, (iii) thromboxane inhibitors and receptor antagonists and (iv) platelet membrane glycoprotein receptor antagonists; (b) inhibitors of cell adhesion molecules, including (i) selectin inhibitors and (ii) integrin inhibitors; (c) anti-chemotactic agents; (d) interleukin receptor antagonists; and (e) intracellular signaling inhibitors selected from the group consisting of (i) protein kinase C inhibitors and protein tyrosine kinase inhibitors, (ii) modulators of intracellular protein tyrosine phosphatases, and (iii) inhibitors of src homology₂ domains, the concentration of each agent within the solution being the concentration of that agent which is desired to be delivered locally to an operative vascular site in order to achieve a level of inhibitory effect at the operative vascular site and that is less than a concentration which would be required to provide the same level of inhibitory effect at the operative vascular site if the solution was applied systemically.

41. The solution of Claim 40, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 100,000 nanomolar.

42. The solution of Claim 40, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 10,000 nanomolar.

43. The solution of Claim 40, wherein the liquid carrier comprises an irrigation fluid.

44. The solution of Claim 40, wherein the liquid carrier is selected from the group consisting of a biocompatible solvent, a suspension, a polymerizable or non-polymerizable gel, a paste and a salve.

45. The solution of Claim 40, wherein the solution includes at least one spasm inhibitory agent.

46. The solution of Claim 45, wherein the at least one spasm inhibitory agent is selected from the group consisting of: serotonin₂ receptor subtype antagonists; tachykinin receptor antagonists; nitric oxide donors; ATP-sensitive potassium channel openers; calcium channel antagonists; and endothelin receptor antagonists.

47. The solution of Claim 46, wherein the at least one spasm inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin₂ receptor antagonists; 0.1 to 10,000 nanomolar for tachykinin receptor antagonists; 1.0 to 10,000 nanomolar for nitric oxide donors; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; 1.0 to 10,000 nanomolar for calcium channel antagonists; and 0.01 to 100,000 nanomolar for endothelin receptor antagonists.

48. The solution of Claim 40, wherein the solution includes at least one pain/inflammation inhibitory agent.

49. The solution of Claim 48, wherein the at least one pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin₁ receptor subtype antagonists and neurokinin₂ receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA₂ isoform inhibitors and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipoxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 receptor subtype antagonists and eicosanoid EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene

receptor antagonists including leukotriene B₄ receptor subtype antagonists and leukotriene D₄ receptor subtype antagonists; opioid receptor agonists including μ -opioid receptor subtype agonists, δ -opioid receptor subtype agonists, and κ -opioid receptor subtype agonists; purinoceptor agonists and antagonists including P_{2Y} receptor agonists and P_{2X} receptor antagonists; and ATP-sensitive potassium channel openers.

50. The solution of Claim 49, wherein the at least one pain/inflammation inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.01 to 1,000 nanomolar for histamine receptor antagonists; 0.1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin₁ receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin₂ receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for PLA₂ isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B₄ receptor subtype antagonists; 0.1 to 500 nanomolar for μ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for δ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for κ -opioid receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; and 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers.

51. A solution for use in the preemptive inhibition of restenosis during a vascular procedure, comprising a plurality of restenosis inhibitory agents in a liquid carrier, the agents being selected to act on a plurality of differing molecular targets, the concentration of each agent within the solution being the concentration of that agent which is desired to be delivered locally to an operative vascular site in order to achieve a level of inhibitory effect at the operative vascular site and that is less than a concentration which would be required to provide the same level of inhibitory effect at the operative vascular site if the solution was applied systemically.

52. The solution of Claim 51, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 100,000 nanomolar.

53. The solution of Claim 51, wherein each of the plurality of agents in the solution is included at a concentration of no greater than 10,000 nanomolar.

54. The solution of Claim 51, wherein the liquid carrier comprises an irrigation fluid.

55. The solution of Claim 51, wherein the liquid carrier is selected from the group consisting of a biocompatible solvent, a suspension, a polymerizable or non-polymerizable gel, a paste and a salve.

56. The solution of Claim 51, wherein the solution includes at least one spasm inhibitory agent.

57. The solution of Claim 56, wherein the at least one spasm inhibitory agent is selected from the group consisting of: serotonin₂ receptor subtype antagonists; tachykinin receptor antagonists; nitric oxide donors; ATP-sensitive potassium channel openers; calcium channel antagonists; and endothelin receptor antagonists.

58. The solution of Claim 57, wherein the at least one spasm inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin₂ receptor antagonists; 0.1 to 10,000 nanomolar for tachykinin receptor antagonists; 1.0 to 10,000 nanomolar for nitric oxide donors; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; 1.0 to 10,000 nanomolar for calcium channel antagonists; and 0.01 to 100,000 nanomolar for endothelin receptor antagonists.

59. The solution of Claim 51, wherein the solution includes at least one pain/inflammation inhibitory agent.

60. The solution of Claim 59, wherein the at least one pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin₁ receptor subtype antagonists and neurokinin₂ receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA₂ isoform inhibitors and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 receptor subtype antagonists and eicosanoid EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B₄ receptor subtype antagonists and leukotriene D₄ receptor subtype antagonists; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinceptor agonists and antagonists including P_{2Y} receptor agonists and P_{2X} receptor antagonists; and ATP-sensitive potassium channel openers.

61. The solution of Claim 60, wherein the at least one pain/inflammation inhibitory agent is included at a concentration of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.01 to 1,000 nanomolar for histamine receptor antagonists; 0.1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin₁ receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin₂ receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for PLA₂ isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B₄ receptor subtype antagonists; 0.1 to 500 nanomolar for μ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for δ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for κ -opioid receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; and 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers.

62. The solution of Claim 51, wherein the restenosis inhibitory agents are selected from the group consisting of: antiplatelet agents including thrombin inhibitors and receptor antagonists, purinoceptor antagonists, thromboxane inhibitors and receptor antagonists and platelet membrane glycoprotein receptor antagonists; inhibitors of cell adhesion molecules, including selectin inhibitors and integrin inhibitors; anti-chemotactic agents; interleukin receptor antagonists; and intracellular signaling inhibitors including protein kinase C inhibitors and protein tyrosine kinase inhibitors, modulators of intracellular protein tyrosine phosphatases, inhibitors of src homology₂ domains, and calcium channel antagonists.

63. The solution of Claim 51, wherein the restenosis inhibitory agents are selected from the group consisting of: (a) antiplatelet agents selected from the group consisting of (i) direct thrombin inhibitors and receptor antagonists, (ii) purinoceptor receptor antagonists, (iii) thromboxane inhibitors and receptor antagonists and (iv) platelet membrane glycoprotein receptor antagonists; (b) inhibitors of cell adhesion molecules, including (i) selectin inhibitors and (ii) integrin inhibitors; (c) anti-chemotactic agents; (d) interleukin receptor antagonists; and (e) intracellular signaling inhibitors selected from the group consisting of (i) protein kinase C inhibitors and protein tyrosine kinase inhibitors, (ii) modulators of intracellular protein tyrosine phosphatases, and (iii) inhibitors of src homology₂ domains.

64. The solution of Claim 51, wherein each of the plurality of agents in the solution applied is included at a concentration that is sufficient to provide a level of inhibitory effect at the operative vascular site when locally applied, and that is less than a concentration which would be required to provide the same level of inhibitory effect at the operative vascular site if applied systemically.